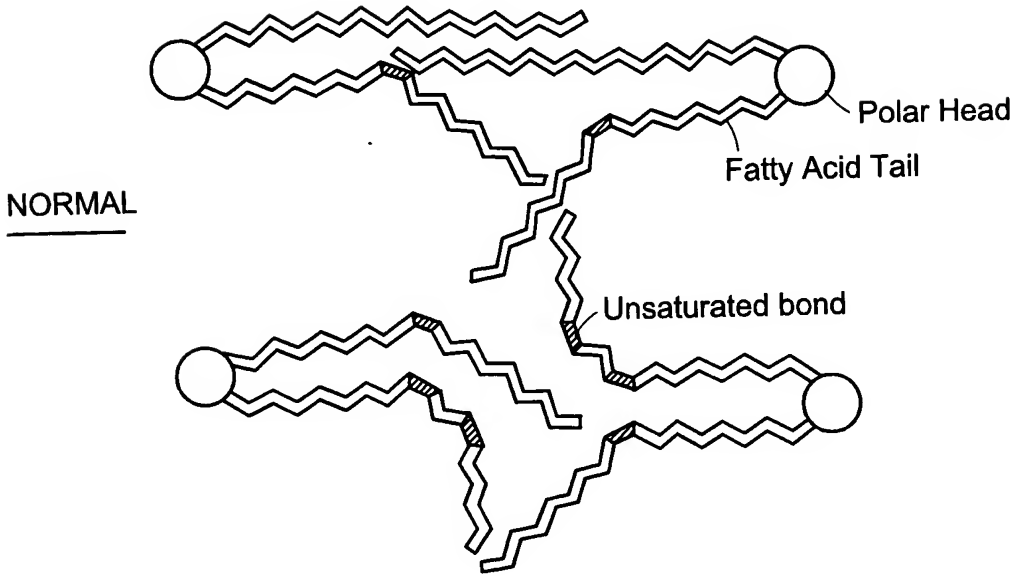


Consequences of Oxidative Agents Attacking Membranes

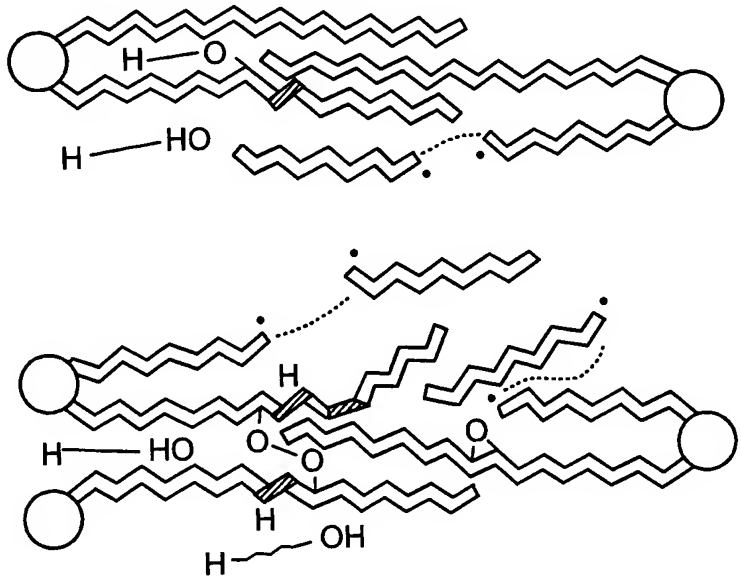


FIG. 1

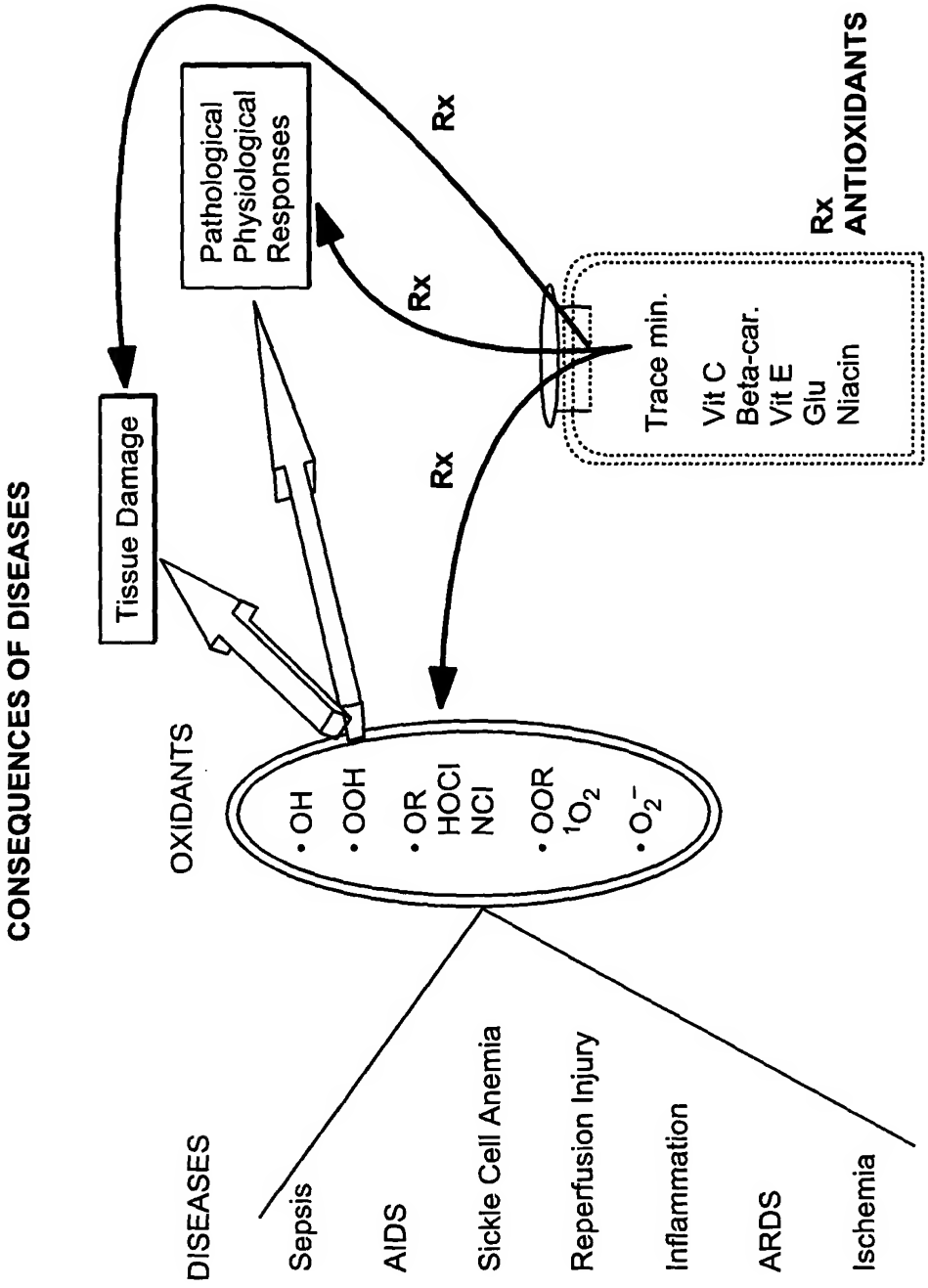
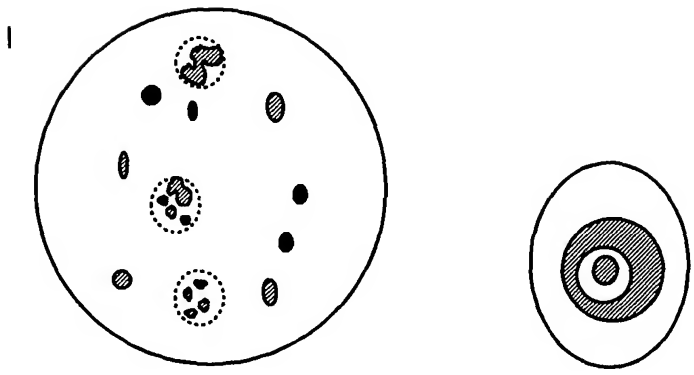
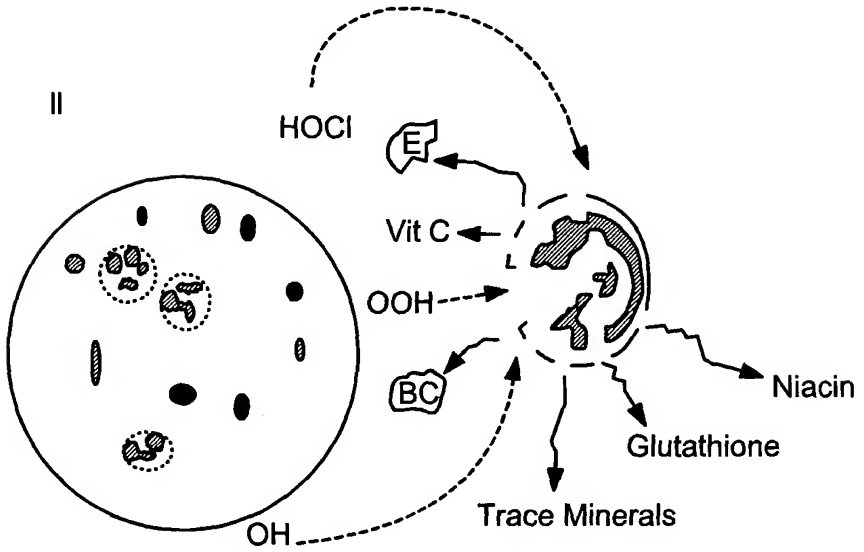

CONSEQUENCES OF DISEASES
Tissue Damage
Pathological Physiological Responses
Rx
Rx
Rx
Rx ANTIOXIDANTS
Trace min.
Vit C
Beta-car.
Vit E
Glu
Niacin
OXIDANTS
•OH
•OOH
•OR
HOCl
NCl
•OOR
$^1O_2$
$\cdot O_2^-$
DISEASES
Sepsis
AIDS
Sickle Cell Anemia
Reperfusion Injury
Inflammation
ARDS
Ischemia

FIG. 2



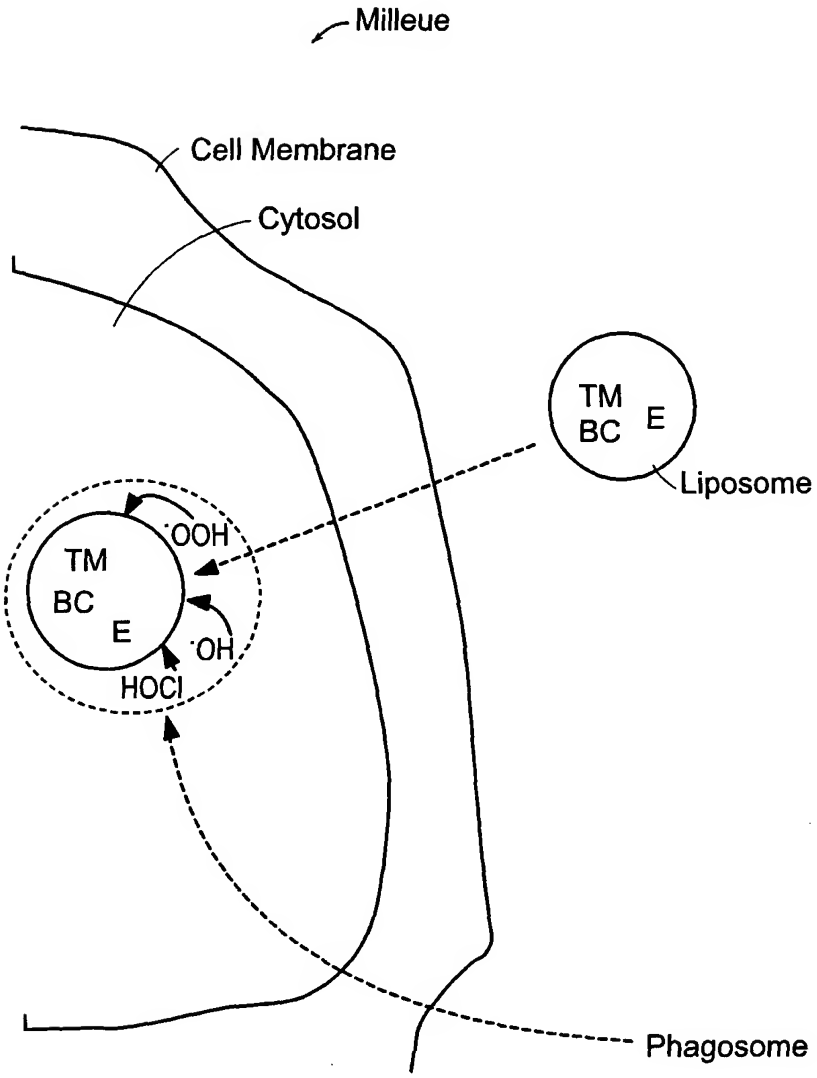
No liberation of oxidants

FIG. 3A



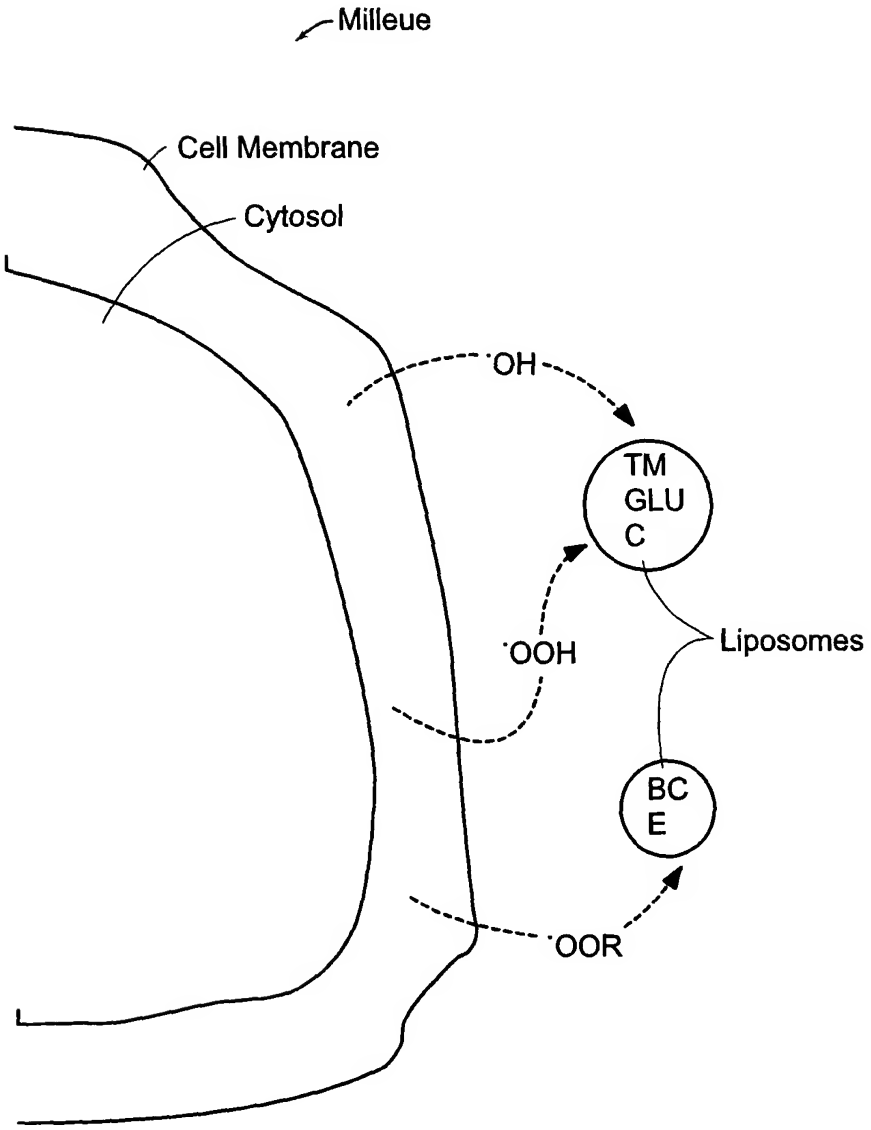
Oxidants liberated into the microenvironment, and subsequently attacking liposomes.
Antioxidants also liberated into the microenvironment, after rupture of liposomes.

FIG. 3B



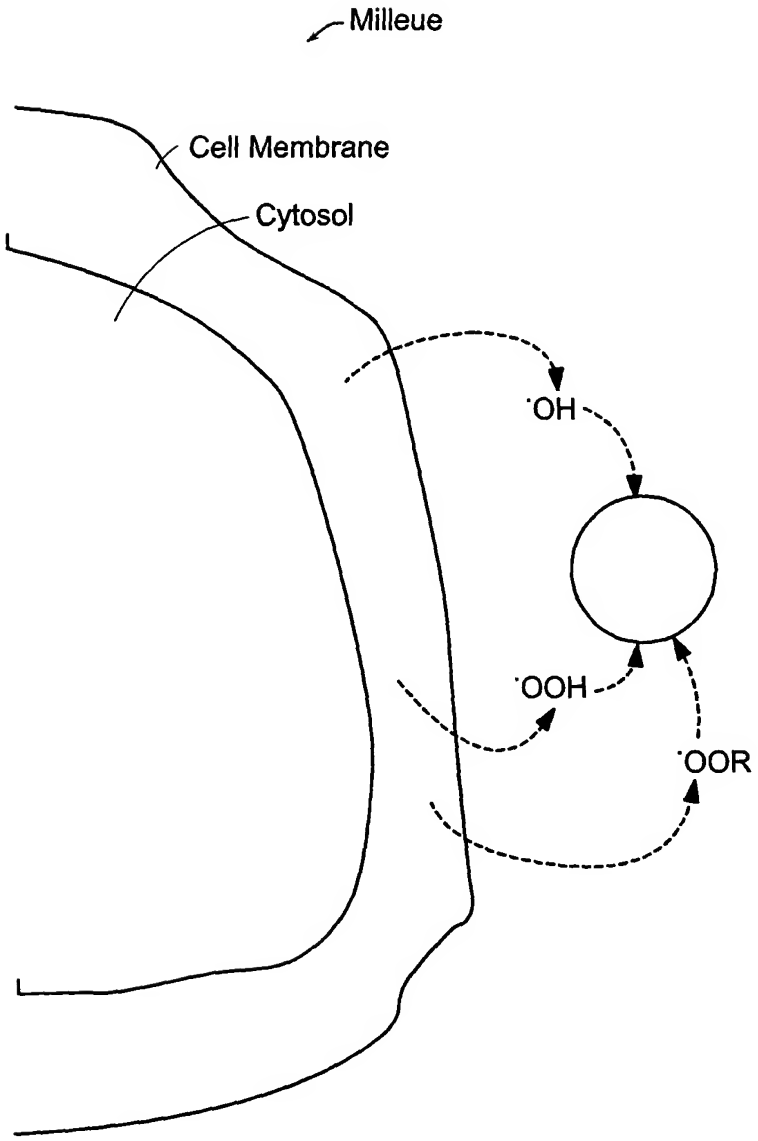
The liposome may undergo peroxidation on entrance through the cell membrane or within the cell itself

FIG. 4



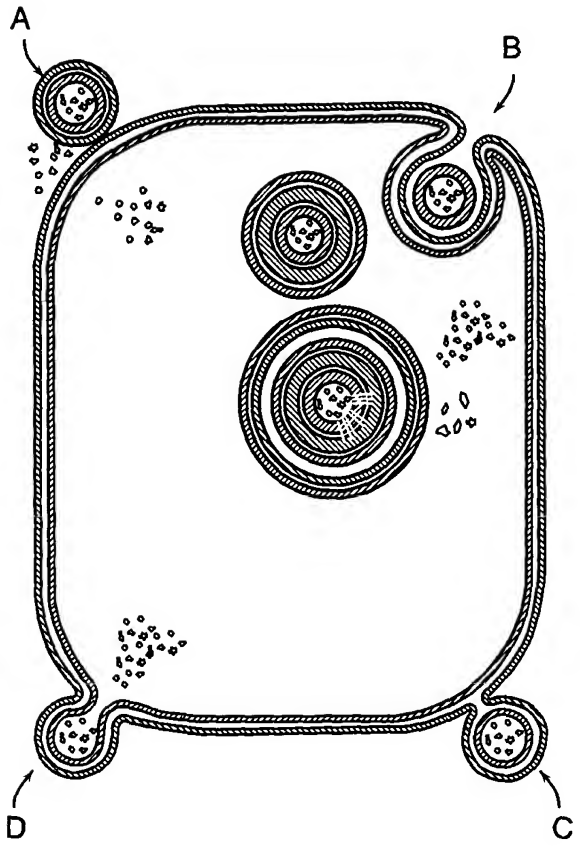
Liposomes in the proximity of a cellular membrane undergoing peroxidation. The liposomes once adjacent to the membrane, would then also undergo peroxidation with release of antioxodants. The anti-oxidants will quench the free radicals and abate futher membrane damage.

FIG. 5



Oxidants occuring within the cell membrane attack the liposomal membrane. Oxidants would then be erradicated preventing further tissue damage.

FIG. 6



A- adsorbed liposome

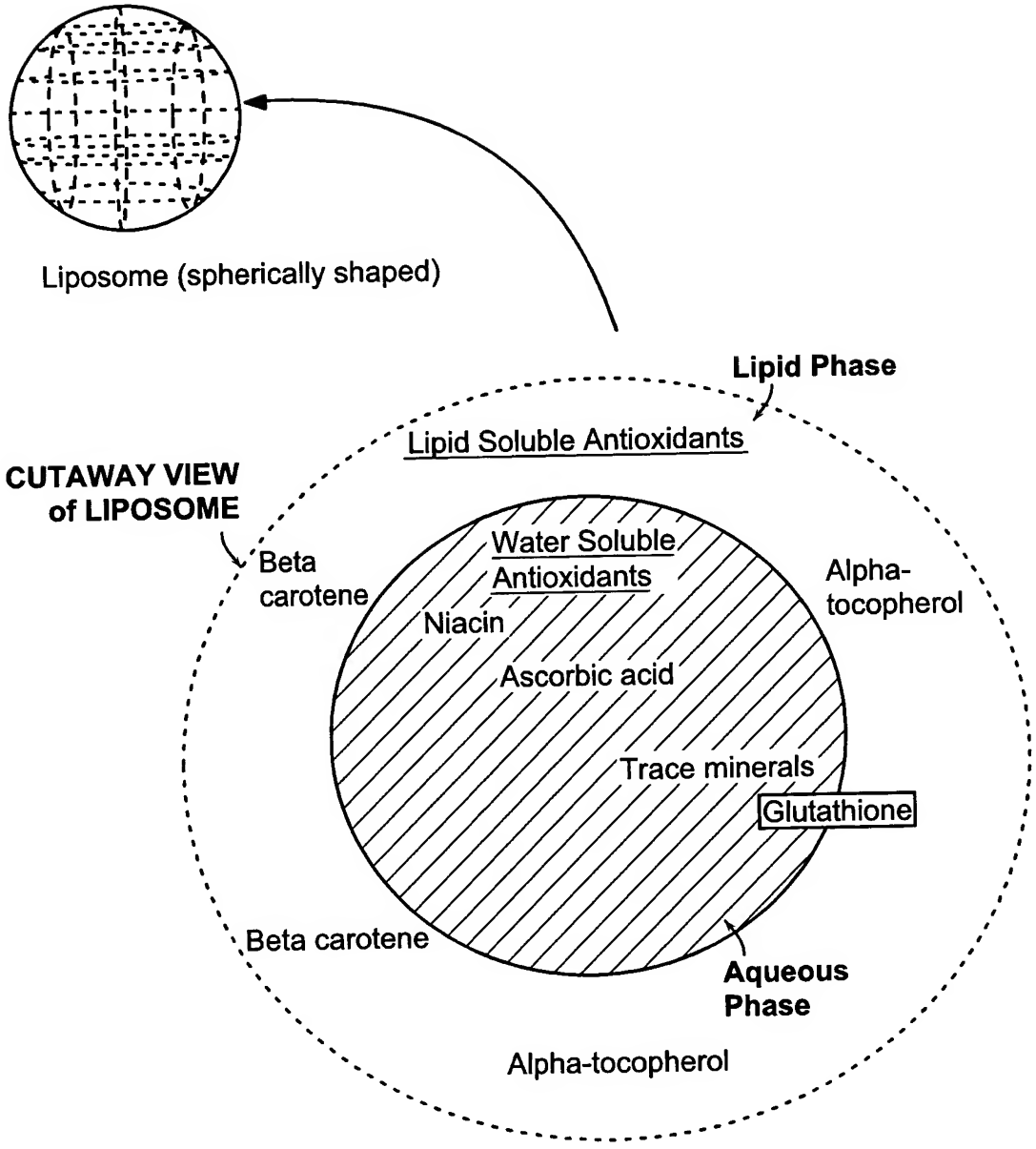
B- Liposome undergoing endocytosis

C- Liposome undergoing lipid exchange

D- Fused liposome

E- Cell membrane undergoing peroxidation with subsequent peroxidation of liposomes (not shown, see Fig.6)

FIG. 7



***Glutathione exhibits both lipophilic and hydrophilic properties

FIG. 8

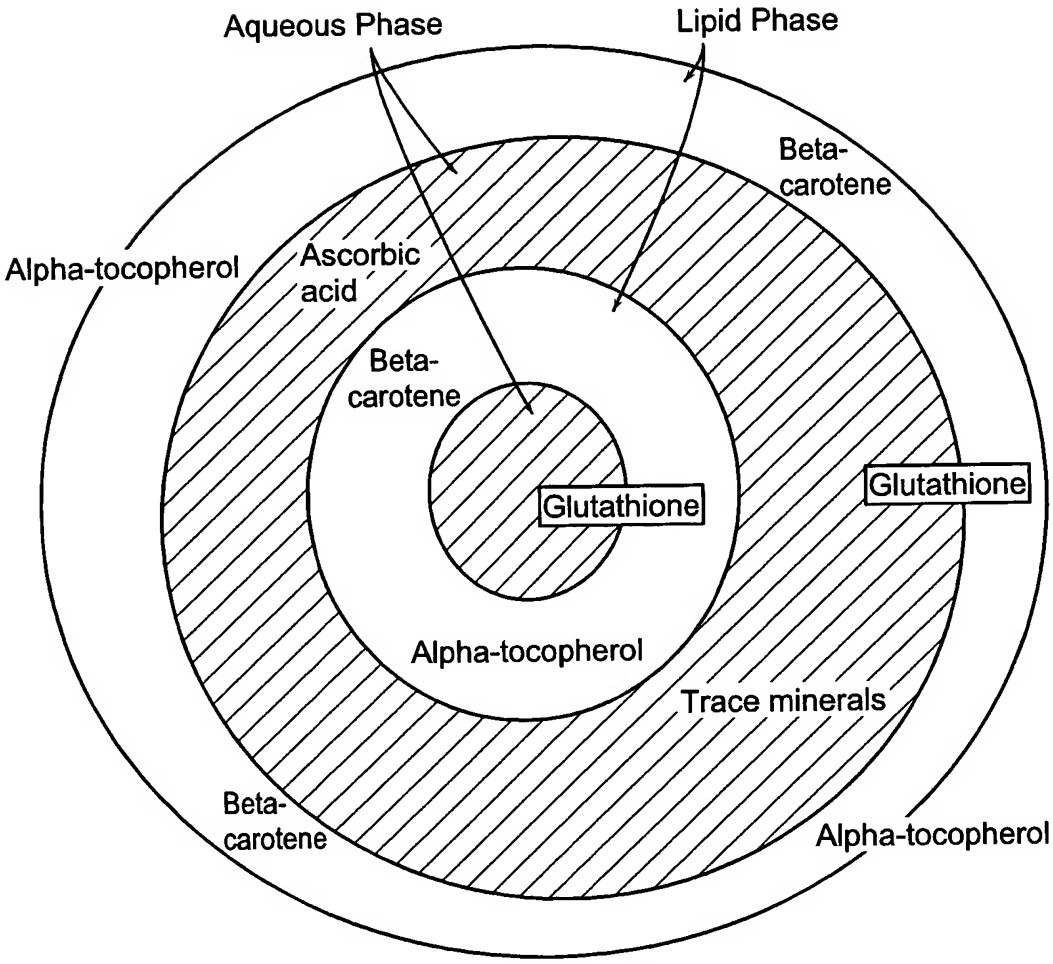
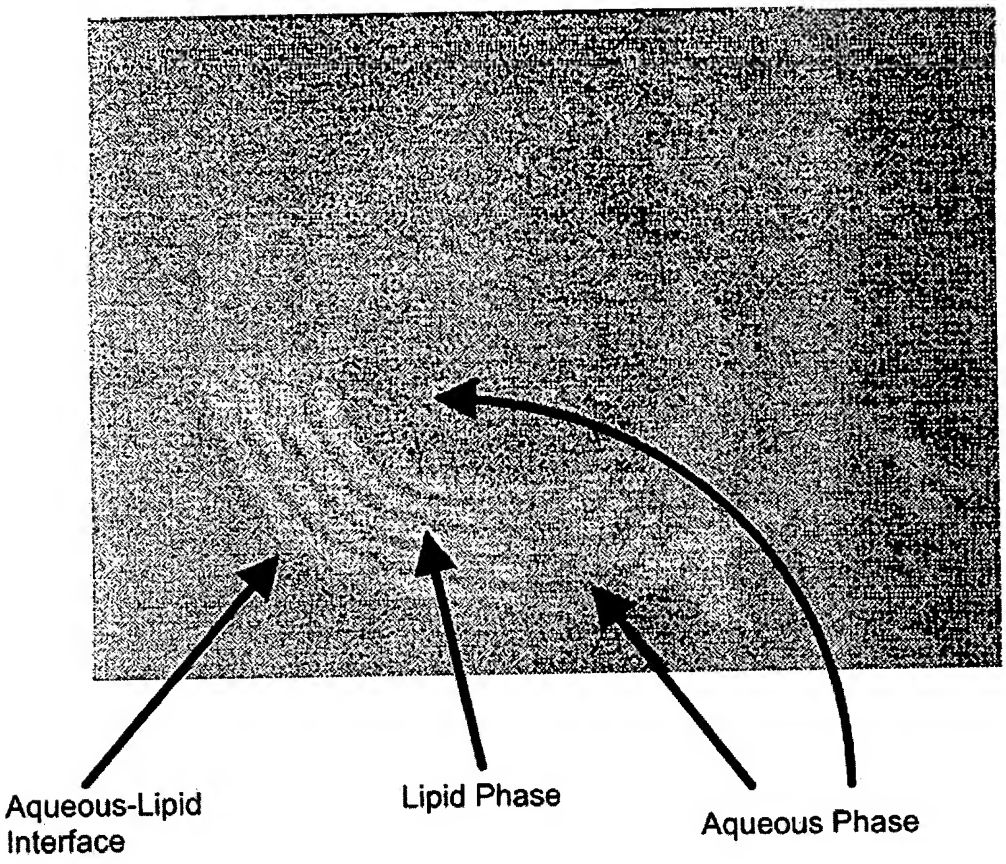

Aqueous Phase
Lipid Phase
Beta-carotene
Alpha-tocopherol
Ascorbic acid
Beta-carotene
Glutathione
Glutathione
Alpha-tocopherol
Trace minerals
Beta-carotene
Alpha-tocopherol

FIG. 9

Inventor: Milton G. Smith
U.S.S.N.: Not Yet Assigned
Title: Method to Reduce Free Radical-Mediated...
Docket No.: 62157.010111
Greenberg Traurig, LLP
Telephone: (617) 310-6000



The dark areas are the aqueous phase, and the light areas are lipid. Lipid soluble antioxidants would be found in the lipid phase and water soluble antioxidants would be found in the aqueous phase.

FIG. 10

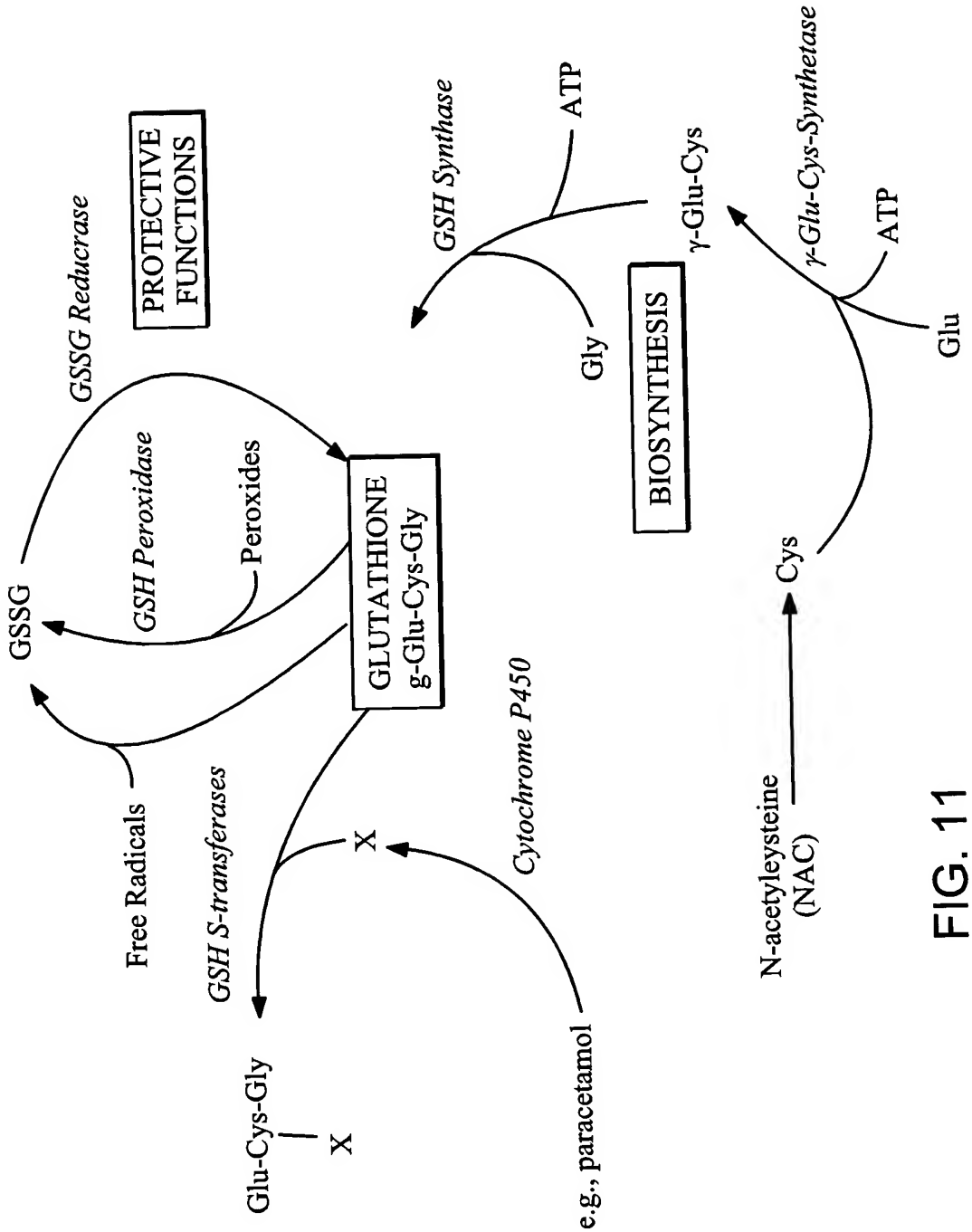
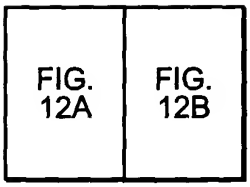

PROTECTIVE FUNCTIONS
GSSG Reducrase
GSSG
GSH Peroxidase
Peroxides
Free Radicals
GLUTATHIONE
g-Glu-Cys-Gly
GSH S-transferases
X
Glu-Cys-Gly
X
Cytochrome P450
e.g., paracetamol
GSH Synthase
ATP
Gly
BIOSYNTHESIS
γ-Glu-Cys
γ-Glu-Cys-Synthetase
ATP
Glu
Cys
N-acetyleysteine
(NAC)

FIG. 11

FIG. 12



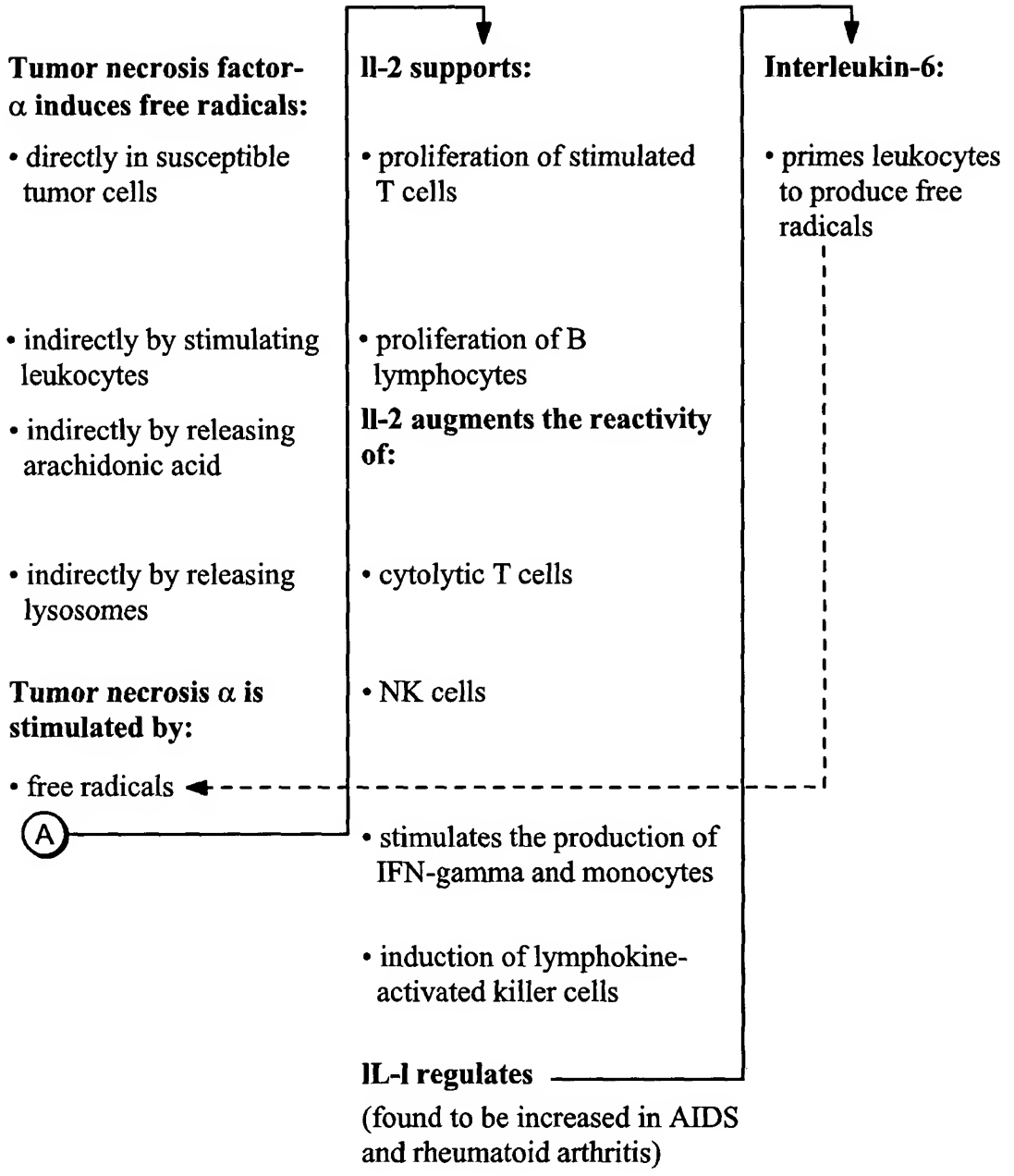
T cell function:

- induction of NK cell function
- induction of cytotoxic T cell function
- secretion of factors which induce non-lymphoid cell function
- induction of suppressor cell function
- secretion of growth and differention factors for lymphoid cells
- secretion of hematopietic colony stimulating factors
- activation of macrophages
- induction of B cell function

Glutathione regulates:

- CD4 and CD8 receptors
- PGE2 synthesis (& other PGs)
- macrophage phagocytosis
- leukotriene C production
- T cell proliferation
- glutathione peroxidase function in macrophages
- DNA synthesis
- blast formation
- IL-2 receptors (alpha chain) → (A)
- NF-KB transcription for cytokines and proteins involved in the inflammatory process
- the affinity of NF-KB to DNA
- the dimerization of the HIV tat protein or the conformational changes in the tat protein(?)

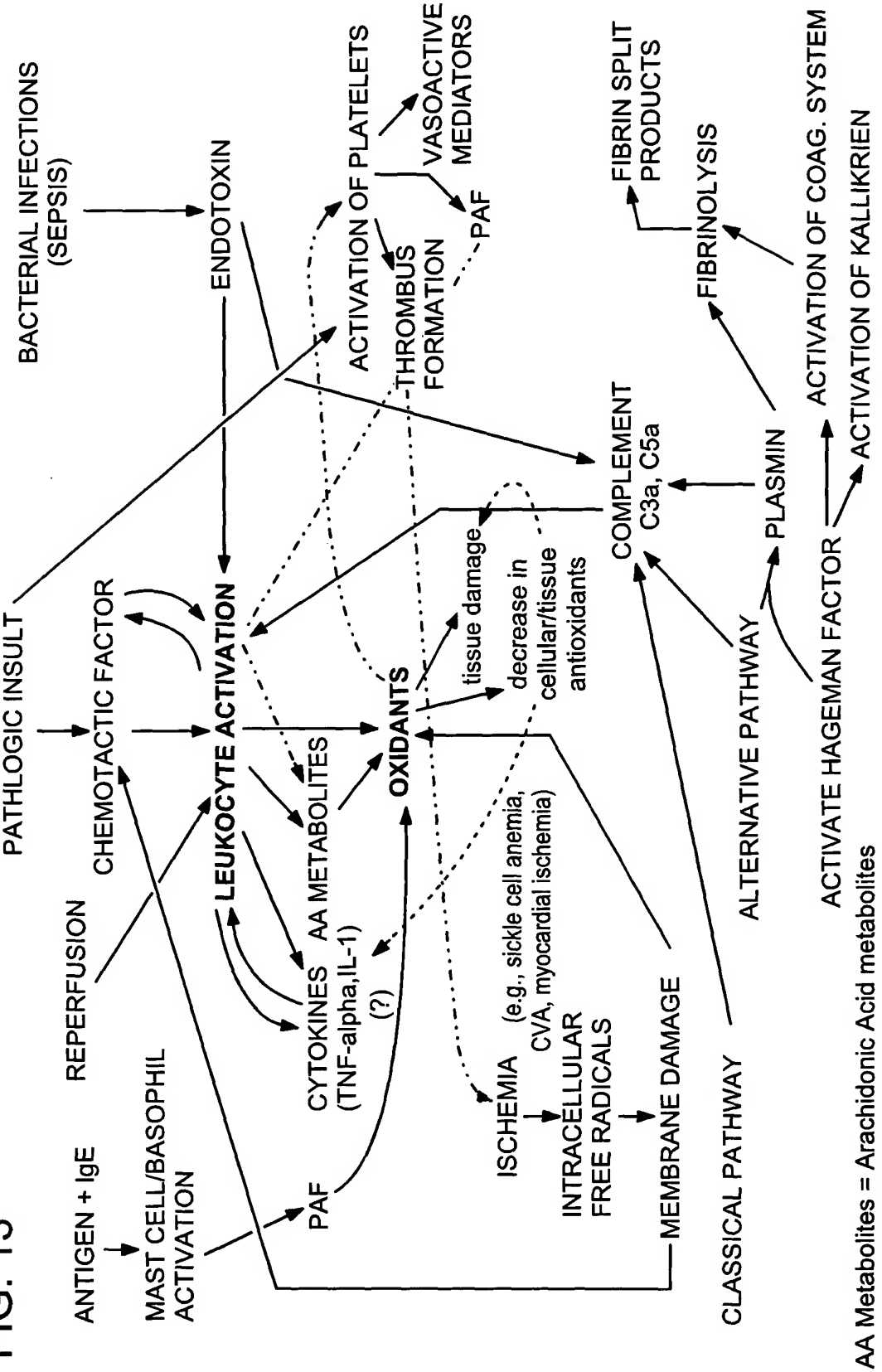
FIG. 12A

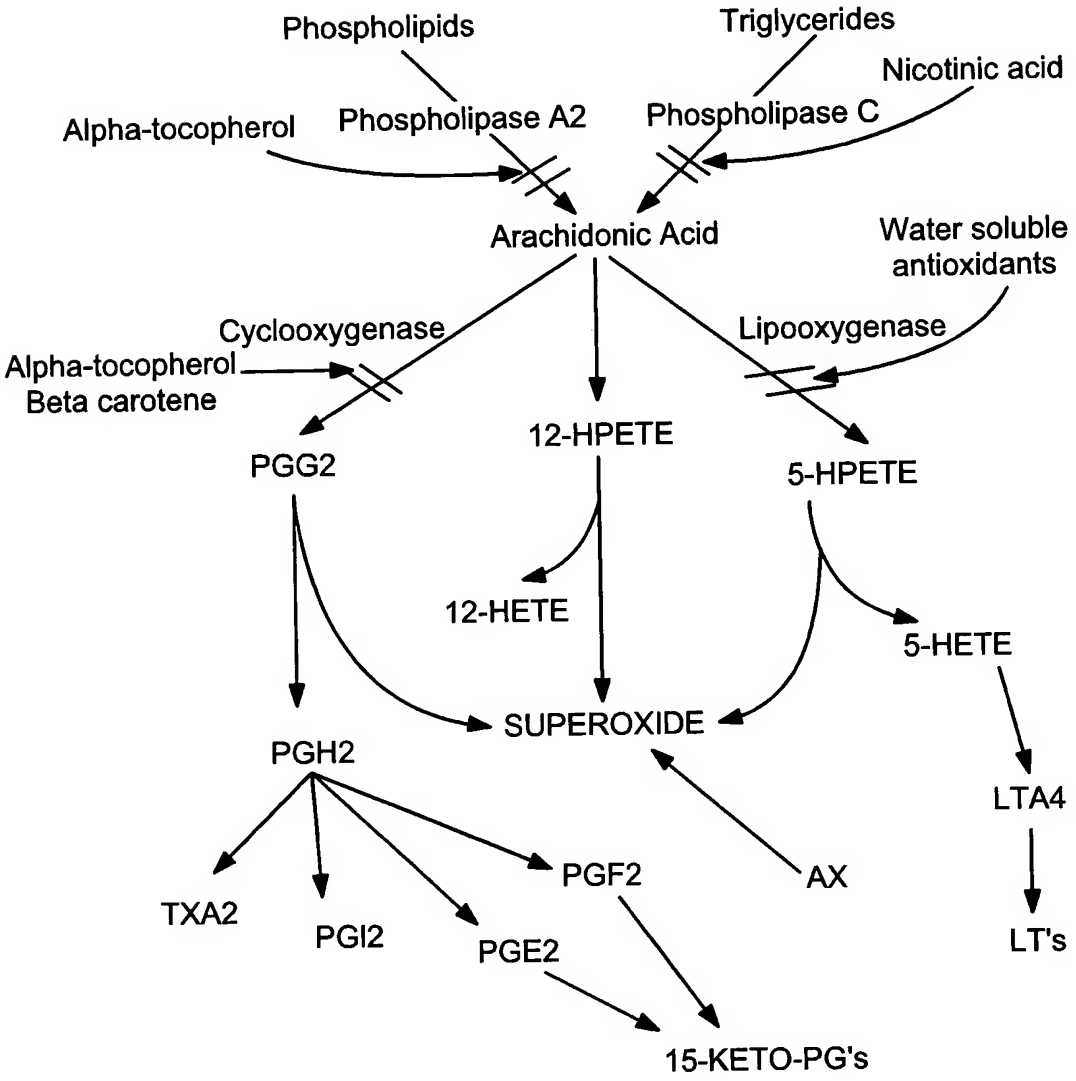


Glutathione decreased in AIDS
TNF-alpha increased in AIDS, Sepsis, Burns
IL-6 increased in AIDS

FIG. 12B

FIG. 13


BACTERIAL INFECTIONS (SEPSIS)
ENDOTOXIN
ACTIVATION OF PLATELETS
VASOACTIVE MEDIATORS
THROMBUS FORMATION
PAF
FIBRIN SPLIT PRODUCTS
FIBRINOLYSIS
COMPLEMENT C3a, C5a
PLASMIN
ACTIVATION OF COAG. SYSTEM
ACTIVATION OF KALLIKRIEN
ACTIVATE HAGEMAN FACTOR
ALTERNATIVE PATHWAY
CLASSICAL PATHWAY
PATHLOGIC INSULT
CHEMOTACTIC FACTOR
LEUKOCYTE ACTIVATION
OXIDANTS
tissue damage
decrease in cellular/tissue antioxidants
AA METABOLITES
CYTOKINES (TNF-alpha,IL-1) (?)
REPERFUSION
ANTIGEN + IgE
MAST CELL/BASOPHIL ACTIVATION
PAF
ISCHEMIA (e.g., sickle cell anemia, CVA, myocardial ischemia)
INTRACELLULAR FREE RADICALS
MEMBRANE DAMAGE
AA Metabolites = Arachidonic Acid metabolites



AX = antioxidants

FIG. 14

Fig. 15

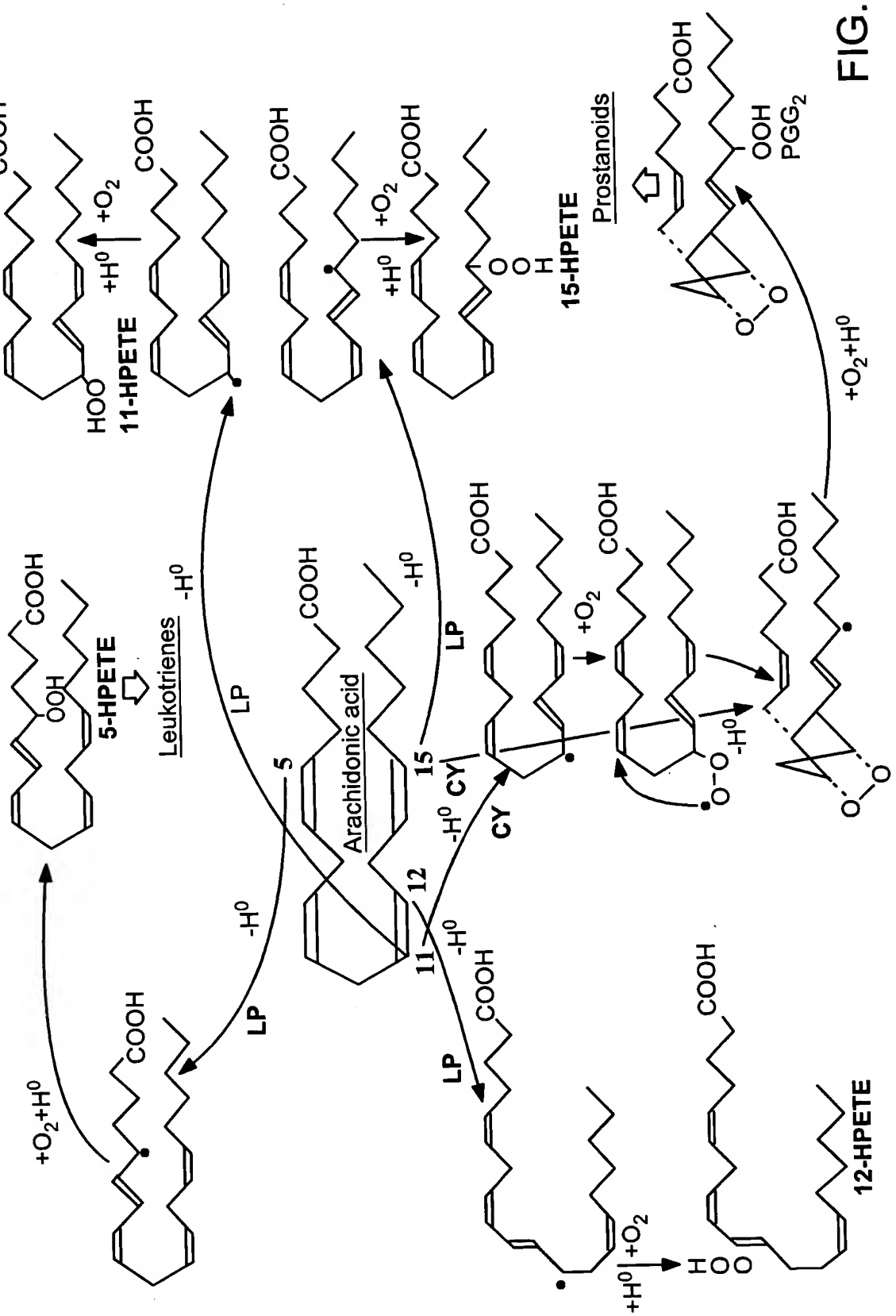

COOH
OOH
5-HPETE
Leukotrienes
$-H^0$
LP
5
Arachidonic acid
11
12
15
$+O_2+H^0$
$+O_2$
$+H^0$
HOO
11-HPETE
O
O
H
15-HPETE
Prostanoids
OOH
PGG_2
CY
$-H^0$ CY
12-HPETE

FIG. 15

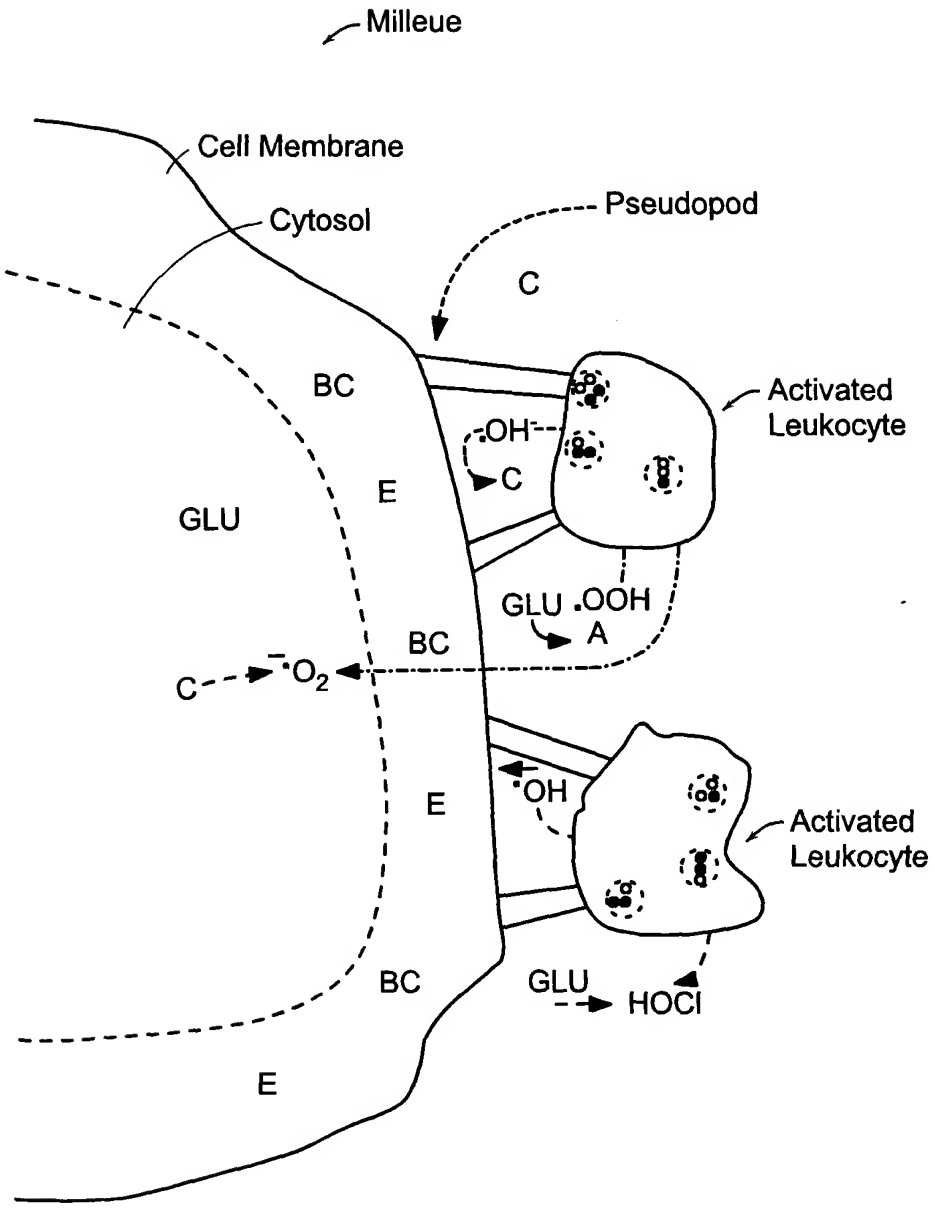
Prostaglandin Metabolites; Enzymes and Their Inhibitors

Key to abbreviations:

PGG2 - Prostaglandin G2
PGH2 - Prostaglandin H2
TXA2 - Thromboxane A2
PGI2 - Prostaglandin I2
PGE2 - Prostaglandin E2
PGF2 - Prostaglandin F2
15-Keto-PG's - 15- Keto- Prostaglandins
12-HPETE - 12- Hydroperoxy eicosatetraenoic acid
12-HETE - 12- Hydroxyeicosate-traenoic acid
5-HPETE - 5- Hydroperoxy eicosatetraenoic acid
5-HETE - 5- Hydroxyeicosate-traenoic acid
LTA4 - Leukotriene A4
LT's - Leukotrienes (types B4, C4, D4, E4)

Enzymes	Enzyme Inhibitors	
Phospholipase A2	Alpha-tocopherol	(fat soluble)
Phospholipase C	Nicotinic acid	(Water soluble)
Cyclooxygenase	Alpha-tocopherol and beta-carotene	(fat soluble)
Lipooxygenase	Glutathione and ascorbic acid	(Water soluble)

FIG. 16



Activated leukocytes liberating oxidants, but cellular membrane is protected by the prescience of fat and water soluble antioxidants.

FIG. 17